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Chorioamnionitis and Neonatal Encephalopathy in Term Infants With Fetal Acidemia: Histopathologic Correlations

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The aim of this study was to determine whether the presence or severity of histologic abnormalities of infection/inflammation such as chorioamnionitis, vasculitis, or funisitis confers an additional risk for neonatal encephalopathy in term infants delivered in the presence of severe fetal acidosis. The medical records as well as placental pathology of term infants (n = 51) born with a cord umbilical arterial pH <7.00 were reviewed. Abnormal outcome was predefined as Sarnat stage 2 or 3 neonatal encephalopathy in the first week of life or neonatal death as a consequence of severe brain injury.

Consistent with prior data, the presence of severe fetal acidemia, a low 5-minute Apgar score, and need for cardiopulmonary resuscitation were significantly associated with neonatal encephalopathy. However, the presence of histologic chorioamnionitis had a poor predictive value and did not confer additional risk for the subsequent development of neonatal encephalopathy. **© 2005 by Elsevier Inc. All rights reserved.**

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Introduction

There is an increasing body of evidence supporting the association between chorioamnionitis and the development of cerebral palsy [1-3]. However, the overwhelming majority of term infants exposed to chorioamnionitis have an uncomplicated neonatal course and develop normally. Thus it is important to determine those factors and events that increase the risk for brain injury in term newborns born to mothers with chorioamnionitis. Cytokines appear to play an important role in the cascade of events leading to brain injury with infection in term as well as preterm infants [4-6]. Indeed we have previously demonstrated elevated cytokine concentrations in term infants born to mothers with clinical chorioamnionitis, with the highest levels observed in infants who develop encephalopathy or seizures, or both [7]. Because clinical chorioamnionitis markedly underestimates the presence of histologic infection, we questioned whether placental evidence of infection/inflammation would be more predictive of neonatal encephalopathy, particularly in those infants at highest risk for injury, i.e., delivered in the presence of severe fetal acidemia. The objective of this cohort study was to determine the potential additional risk attributed to the presence of histologic chorioamnionitis in relationship to the subsequent development of moderate to severe neonatal encephalopathy in term infants with severe fetal acidemia.

Methods

Study Design

This retrospective cohort study included all infants born at or near term, i.e., with a gestation $\geq$ 36 weeks and a cord umbilical arterial pH $\leq$ 7.00 admitted to the neonatal intensive care unit at Parkland Memorial Hospital between January 2000 to December 2002 and with available placental pathology. The study met Health Insurance Portability Accountability Act requirements, and the institutional review board of the University of Texas Southwestern Medical Center at Dallas approved review of the data.

The medical charts were reviewed, and the following data were recorded: complications during pregnancy and labor, i.e., pregnancy-induced hypertension, evidence of clinical chorioamnionitis based on a maternal fever $>$ 38.5°C, maternal tachycardia, fetal tachycardia $\pm$

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malodorous vaginal discharge, mode of delivery, need for delivery room resuscitation including intensive resuscitation, i.e., the need for chest compressions ± medications, Apgar scores at 1, 5, and 10 minutes, cord umbilical arterial blood gas parameters, initial blood pressure upon admission to intensive care and initial blood sugar (both obtained within the first 30 minutes after admission), presence of moderate to severe encephalopathy, and death.

Abnormal Neurologic Outcome

An abnormal outcome was defined as death secondary to severe neurologic injury or moderate to severe encephalopathy in the first week of life. During the study period, each infant born with a cord umbilical arterial pH <7.00 and admitted to the intensive care nursery underwent a detailed neurologic examination within 6 hours after birth, as part of a neuroprotective study being conducted at the time. The Sarnat staging was used to characterize the degree of encephalopathy as follows: moderate encephalopathy (Sarnat stage 2) characterized by lethargy, hypotonia, and seizures; and severe encephalopathy (Sarnat Stage 3) characterized by stupor, flaccidity, and suppression of brainstem and autonomic functions [8]. Infants where appropriate underwent electroencephalographic recordings and neuroimaging to delineate the extent of brain injury. All infants where appropriate underwent a sepsis evaluation and were administered antibiotics.

Placental Pathology

Placentas were sectioned and processed using standard institutional procedures (two sections each of umbilical cord, membranes, and full thickness parenchyma). For the study, objective assessment and grading of inflammation in the umbilical cord, membranes, and chronic plate was performed by a single pathologist, who was unaware of neonatal outcomes. Histologic evaluation was similar to that described by Salafia et al. [9].

Chorioamnionitis in this study referred to inflammation of the chorionic plate and was grouped as mild (low number of neutrophils in the subchorionic fibrin and chorionic plate) or moderate to severe (multiple foci of neutrophilic infiltrates). Chorionic vasculitis referred to inflammation within fetal vessels, including margination.

Inflammation of the cord was grouped as mild (neutrophilic infiltrates in the umbilical vein, confined to the inner muscle), or true funisitis (full thickness of the muscle or extension of neutrophils into Wharton's jelly).

Statistical Analysis

Data were analyzed with chi-square analysis or Fisher exact test for categorical data and *t* test or Mann-Whitney rank sum test when normality failed for continuous data. Odds ratio was calculated with 95% confidence intervals. Data are presented as mean ± S.D. or median with interquartile ranks (25-75%) for data.

Results

During the study period, 69 infants were admitted to intensive care with an umbilical arterial pH <7.00. Placental pathology was available in 51 (75%) of these cases, and it is this group of infants that forms the basis of the subsequent analysis. The 51 infants were of birth weight 3400 ± 546 grams, and gestation was 39.9 ± 1.4 weeks. Perinatal complications included meconium ± fetal heart rate abnormalities n = 16 (31%), clinical chorioamnionitis n = 6 (12%) (Table 1). The mode of delivery was vaginal n = 15 (29%) (including three via assisted low forceps extraction) and cesarean section n = 36 (71%). Resuscitation in the delivery room included intubation (n = 18) (35%) and cardiopulmonary resuscitation (n = 6) (11%). A 5-minute Apgar score ≤5 was observed in 15 infants (29%). An abnormal outcome, i.e., death (n = 3) or moderate to severe encephalopathy was observed in 15 (29%) infants. In addition, a magnetic resonance imaging study was abnormal in 11 of 12 infants, with findings consistent with acute hypoxic ischemic injury. The sepsis evaluation was negative in all 15 infants with encephalopathy. One of the 36 infants with an unremarkable neonatal neurologic course developed sepsis (*Escherichia coli*), two infants developed persistent pulmonary hypertension of the newborn, and three infants developed transient hypoglycemia.

Table 1. Characteristics of infants with moderate to severe encephalopathy as compared with infants with normal neonatal outcomes

	Abnormal Outcome (n = 15)	Normal Outcome (n = 36)
Birth weight	3516 ± 664	3351 ± 491
Gestation	39.6 ± 1	40 ± 1
Cord pH	6.81 ± 0.09	6.92 ± 0.08*
CO_2	113 ± 20	91 ± 17*
Base deficit	−23 ± 4	−19 ± 3*
Mode of delivery		
Vaginal	4	8
Cesarean section	3	14
Emergent cesarean section	7	12
Forceps	1	2
Perinatal complications		
FTHR alone	5 (33%)	6 (16%)
Meconium alone	1 (7%)	2 (6%)
FTHR + Meconium	6 (40%)	10 (28%)
Clinical chorioamnionitis	1 (7%)	5 (14%)
Abruption	1 (7%)	2 (6%)
Other	1 (7%)	11 (32%)
Delivery room characteristics		
Need of CPR	5 (33%)	1 (3%)*
CPR + Intubation	12 (80%)	12 (33%)*
Apgar <5 at 5 min	13 (87%)	2 (6%)*
Blood sugar <40 (mg/dL)	5 (33%)	4 (11%)
Blood pressure (mm Hg)	42 ± 11	46 ± 11

Abbreviations:
CPR = Cardiopulmonary resuscitation
FTHR = Fetal heart rate tracing abnormality
* $P < 0.005$.

Infants with an abnormal vs normal outcome exhibited a lower pH, i.e., 6.81 ± 0.09 vs 6.92 ± 0.08 ($P < 0.005$), higher arterial carbon dioxide tension, i.e., 113 ± 20 vs 91 ± 17 mm Hg ($P < 0.005$), a greater base deficit, −23 ± 4 vs 19 ± 3 mEq/L ($P < 0.005$), were more likely to receive cardiopulmonary resuscitation, 5 (33%) vs 1 (3%) ($P = 0.006$) and exhibit a 5-minute Apgar score ≤5, i.e., 13 (87%) vs 2 (6%) ($P < 0.0001$). No differences in initial blood sugar and blood pressures were observed between groups.

Histologic chorioamnionitis was observed in 26 (51%) placentas. This was documented in 9 of the 15 infants (60%) with an abnormal outcome as compared with 17 of

the 35 infants (47%) with a normal outcome (not significant) (odds ratio 1.58; confidence interval 0.46, 5.40). The positive predictive value of histologic chorioamnionitis in relation to an abnormal outcome was 30%. Ten cases were classified as mild chorioamnionitis, of whom 2 (20%) developed an abnormal outcome. Sixteen cases were classified as moderate to severe, of whom 7 (44%) developed an abnormal outcome. The positive predictive value of severe chorioamnionitis in relation to abnormal outcome was 37%. Inflammation of the cord was observed in 25 cases. In nine cases it was regarded as mild, of whom 3 (30%) developed an abnormal outcome. Sixteen cases were classified as moderate to severe, of whom 5 (32%) developed an abnormal outcome. The positive predictive value of severe inflammation of the umbilical cord in relation to abnormal outcome was 31% (Table 2). Vasculitis was observed in 19 cases, of whom 7 (40%) developed an abnormal outcome. The positive predictive value of vasculitis in relation to abnormal outcome was 37%.

Discussion

The data in this report indicate that a diagnosis of histologic infection/inflammation of the placenta irrespective of the degree of severity in a high-risk group of term infants, i.e., delivered in the presence of severe fetal acidemia, is a poor predictor of the subsequent development of moderate to severe neonatal encephalopathy. However, consistent with other reports, the need for delivery room cardiopulmonary resuscitation and a 5-minute Apgar score <5 were both significantly associated with abnormal neonatal outcome [10,11].

Chorioamnionitis has been linked to the developmental of cerebral palsy [1-4]. In a recent meta-analysis which included 19 published studies on clinical chorioamnionitis and 7 with histologic chorioamnionitis, the overall relative risk relative risk for linking this association was 4.7 with a confidence interval of 1.3-16.7 [3]. However, the majority of these publications have largely focused on preterm infants, because they are at higher risk for developing cerebral palsy, and only one study has specifically addressed this issue in term infants [5]. Several mechanisms have been proposed to explain the association between chorioamnionitis and brain injury; these include an inflammatory cytokine response, placental inflammation leading to impaired placental perfusion and gas exchange, an intrauterine infection with bacteremia leading to direct involvement of the brain, or fever associated with the infection itself, exacerbating the primary insult to the brain [12].

Table 2. Histopathalogic abnormalities and neonatal encephalopathy in term infants with significant fetal acidemia

	Abnormal Outcome (n = 15)	Normal Outcome (n = 36)	Odds Ratio (95% CI)
Chorioamnionitis			
Mild	2	8	1.7 (0.5-5.7)
Severe	7	9	1.8 (0.5-6.7)
Cord Inflammation			
Mild	3	6	1.3 (0.4-4.3)
Severe	5	11	1.1 (0.3-4.1)
Vasculitis			
Yes	7	12	1.8 (0.5-6.0)
No	8	24	

Abbreviation:
CI = Confidence interval

In the present study of term infants born with severe fetal acidemia, occult placental abnormalities indicative of infection/inflammation were observed in half of the cases. However, such findings alone were poorly predictive of neonatal encephalopathy. Moreover, because the majority of infants with moderate encephalopathy develop normally, inflammation of the placenta would not appear to be the link that bridges chorioamnionitis and long-term neurologic outcomes. It could be argued that this lack of association might reflect the small sample size; however, we consider this less likely given the high-risk nature of the cohort.

The fetal inflammatory response would seem to be a more likely explanation for linking maternal infection and brain injury in the term infant. Thus Smulian et al. reported elevated interleukin-6 levels in both the maternal and fetal compartments with maternal fever [13]. Interestingly concomitant histologic abnormalities were present in only one third of cases, but in these cases there was further amplification of the cytokine response. Extending these observations, we recently demonstrated a significant relationship between the cytokine response and, in particular, elevated serum levels of interleukin-6, interleukin-8, and RANTES and the neonatal neurologic examination in term infants born to mothers with clinical chorioamnionitis [7]. Thus there was a progressive amplification of cytokine response that paralleled a progressive worsening of the neurologic examination, with the highest cytokine levels observed in those infants with encephalopathy or seizures.

In the preterm infant, an inconsistent relationship has also been observed between chorioamnionitis or cytokine release and abnormal neurologic outcome [14-19]. Thus, in some studies, histologic chorioamnionitis has been associated with increased periventricular echodensities, white matter echolucencies, intraventricular hemorrhage, and seizures [14,15]. In addition, funisitis has been demonstrated to be strongly associated with the development of cerebral palsy [14]. Higher amniotic fluid concentrations of interleukin-6 and interleukin-8 have been observed in infants with cerebral palsy as compared with control infants, with the highest levels observed in those cases with funisitis [15]. However, several studies reported an inconsistent or no relationship between cytokines and cranial ultrasound abnormalities or cerebral palsy in premature infants [16-18]. Moreover, a recent study failed to demonstrate any difference in preterm infants who developed cerebral palsy as compared with control infants, with regard to the presence or absence of clinical or histologic chorioamnionitis including funisitis [19].

Early predictors of neonatal encephalopathy in this high-risk cohort were the need for delivery room cardio-

pulmonary resuscitation and prolonged depression as reflected in a low 5-minute Apgar score. These findings are consistent with previous studies in which the need for cardiopulmonary resuscitation was associated with 234-fold increased risk of an abnormal neurologic outcome [10].

Conclusion

Of the 51 infants studied, 15 (29%) developed an abnormal outcome and 31 (71%) had an uncomplicated neonatal course. Histologic chorioamnionitis was observed in 26 (51%) infants (abnormal outcome n = 9 (60%), normal n = 17 (47%). Of these, clinical chorioamnionitis was observed in 6 (12%) infants (abnormal [n = 1], normal]n = 5]) (NS). The positive predictive value of histologic chorioamnionitis was 34%. The severity of chorioamnionitis or fetal vasculitis did not influence the predictive values for abnormal outcome. Infants with abnormal vs normal outcome had a lower cord pH 6.81 ± 0.09 vs 6.92 ± 0.08, greater base deficit −23 ± 4 vs −19 ± 32, a 5-minute Apgar score <5, i.e., 13/15 vs 2/36, required more cardiopulmonary resuscitation 5/15 vs 1/36 ($P = 0.0004$). By multiple logistic regression, only the need of cardiopulmonary resuscitation and a 5-minute Apgar score <5 were related to neonatal encephalopathy ($P < 0.001$).

The data indicate that the presence of histologic chorioamnionitis is a poor marker for the subsequent development of neonatal encephalopathy in an already high-risk group of infants. These observations have to be tempered by the lack of concurrent cytokine measurements and the absence of long-term follow-up data. Future studies in high-risk term infants need to incorporate placental findings as well concurrent determination of the fetal inflammatory cytokine response. In addition, it may be likely in the future to assess for genetic polymorphisms in order to better delineate the risk for brain injury in the presence of placental inflammation in any one individual infant.

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